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Esophageal Diseases

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Introduction

From May 3–6, 2014, in Chicago, IL, investigators gathered from around the world to share discoveries in esophageal diseases. Presentations ranged from advances in endoscopic techniques to non-invasive disease stratification and results from long-term cohort studies. Below, we present the results of seven seminal studies in esophageal diseases reported at DDW 2014. While this work is impressive in its scope and potential for clinical impact, selection of these studies as the “most important” is admittedly somewhat arbitrary, as numerous centers contributed a wealth of new information. With that caveat, below we present our review of the most notable abstracts in esophageal diseases from DDW 2014.

Eosinophilic Esophagitis: New Prospects for Minimally Invasive Evaluation

Patients with eosinophilic esophagitis (EoE) often require many endoscopies during diagnosis and treatment. A patient being worked up according to consensus guidelines will likely receive, at the minimum, an esophagogastroduodenoscopy (EGD) at baseline, another after a trial of proton pump inhibitor (PPI), and a third after starting therapy to demonstrate response. [1] For a patient undergoing dietary elimination therapy with serial food reintroduction, an EGD is typically performed after each food is added back, resulting in an average of nearly five more endoscopies in one recent study.[2] This high number of EGDs results in high costs and increased risk for patients.

At DDW, a group from the Mayo Clinic presented results from a proof-of-concept study using the Cytosponge for minimally invasive evaluation of EoE.[3] The Cytosponge is a novel device consisting of a foam sponge compressed into a gelatin capsule, which is attached to a string.[4] Patients swallow the capsule, but the string is kept dangling from the mouth. In the stomach, the capsule dissolves and releases the sponge. The unconstrained sponge is then retrieved by pulling the string, causing the sponge to move retrograde up the esophagus. The sponge collects cells along the entire length of the esophagus as it exits.

Katzka et al enrolled 20 patients with EoE and performed Cytosponge sampling followed by endoscopy with a routine biopsy protocol to compare the two modalities. Of 16 patients with active EoE on the biopsy protocol (>15 eosinophils per high powered field [eos/hpf]), all had at least 1 eosinophil/hpf on Cytosponge sampling, and 10 had >15 eosinophils/hpf.

(Figure 1) Four patients had more eos/hpf on Cytosponge than on biopsy samples, and one had a Cytosponge demonstrating eosinophils, but biopsies demonstrating no eosinophils. The r value comparing biopsy to Cytosponge was 0.44, indicating a strong positive correlation. Spongiosis and basal cell hyperplasia were visible on Cytosponge samples. There were no complications with the Cytosponge, even though 75% of patients had esophageal strictures. Endoscopists assessed the post-sponge esophagus for abrasion damage, and no significant mucosal abrasions were identified from the Cytosponge. Finally, all patients preferred the Cytosponge to endoscopy.

This study suggests a promising new technology for evaluating EoE with high patient tolerability and a good preliminary safety profile. Given the high cost of endoscopy, and the frequent endoscopies necessary to diagnose and monitor EoE by current guidelines, an inexpensive, less onerous method for monitoring the condition of the esophagus is highly desirable. The eosinophil cell count cutoff for diagnosis of EoE will have to be standardized for Cytosponge sampling, as will the cutoff for successful treatment of EoE, but this technique may have a future role in economical and accurate monitoring of the esophagus for response to treatment of EoE.

Barrett's Esophagus: Wide Area Tissue Sampling and Computer Assisted Analysis Increases Diagnosis

Standard biopsy protocols in Barrett's Esophagus (BE) consist of four quadrant biopsies at one- to two-centimeter intervals throughout the length of the BE.[5] However, this technique leaves most esophageal tissue unsampled, raising the possibility that dysplastic or cancerous tissue may be missed due to sampling error. The abstract presented by Gross et al at the Presidential Plenary Session used wide area tissue sampling (WATS), a technique which combines brush biopsy with computer assisted tissue analysis, to evaluate patients with gastroesophageal reflux disease (GERD) and Barrett's esophagus (BE) receiving care from community gastroenterologists.[6] A total of 2,559 patients underwent WATS followed by traditional forceps biopsy. WATS samples were analyzed using a neural network which sorted over 100,000 cells from each WATS sample, identifying the 200 most abnormal cells for pathologist's review. (Figure 2) Forceps biopsy samples were analyzed using standard histologic techniques. The cohort was predominantly female (60%) with an average age of 55 and had an average BE segment length of < 3 cm. Traditional biopsy identified BE in 377 (15%) of patients and dysplasia in 17 (5% of BE). Adjunctive use of WATS sampling demonstrated BE in an additional 258 (totaling 25% of patients) and found 10 additional cases of dysplasia and one cancer. That represents a 68% increase in BE diagnostic yield and a 65% yield in dysplasia/neoplasia detection. Whether the sensitivity of forceps biopsy was changed by prior brush biopsy was not evaluated, and it is unclear what gold standard should be used for evaluating sensitivity and specificity of WATS. Notably, these findings are bolstered by the results of a systematic review and meta-analysis also presented at this DDW, which found the number needed to treat with WATS to identify one extra case of BE ranged from 4 to 11 and that the increased diagnostic yield for dysplasia was 30% (95% CI 16–55%).[7] These results suggest that WATS can produce improved sensitivity compared to forceps biopsy and that WATS can be successfully used in practice, though the question

of whether the improved performance is attributable to WATS sampling or neural network analysis remains unanswered. Future questions include the impact of these findings on long-term outcomes of patients with BE, and whether these findings are generalizable to practices not participating in clinical trials.

Barrett's Esophagus: Radiofrequency Ablation Decreases Esophageal Adenocarcinoma Risk

The incidence of esophageal adenocarcinoma (EAC) after radiofrequency ablation (RFA) for BE is poorly described, and most previous studies have had too few cancers to generate reliable estimates of cancer risk after RFA treatment. Investigators from the U.S. RFA Registry evaluated the rate of EAC after RFA and the rate of death from EAC, based on the baseline degree of dysplasia prior to treatment.[8] The U.S. RFA Registry cohort consists of 5,521 individuals who received RFA for treatment of BE at 132 sites across the U.S. (approximately 3/4 private practice, 1/4 academic practice). Of these subjects, 5,132 met inclusion criteria of BE length ≥ 1 cm and at least 1 follow-up visit. Nearly half of subjects enrolled in the Registry (48%) had non-dysplastic BE (NDBE) at baseline, while another 48% had dysplasia (21% low-grade (LGD), 19% high-grade (HGD), and 8% indefinite (IND)). (Table 1) The remaining 5% of patients had intramucosal adenocarcinoma (4%) or invasive EAC (1%) and were included only in the mortality rate calculation. Over an average of 2.6 years of follow-up, 100 cases of EAC developed: 3 in patients with NDBE at baseline (0.5 per 1000 person-years [PY]), 2 in IND (2.1 per 1000 PY), 11 in LGD (3.9 per 1000 PY), and 84 in patients with HGD (30.2 per 1000 PY). In patients starting treatment without EAC and receiving at least one RFA, the rate of EAC was 7.8 per 1000 PY. This represents a decrease of at least 50% in every histologic grade compared to historical results and meta-analyses.[9, 10] A second abstract from the Registry demonstrated that most cancers after RFA were intramucosal (56%) and that the majority of those were able to achieve complete eradication of intestinal metaplasia (CEIM) with further endoscopic therapy (69%).[11] In the Registry cohort, 8 of 5,521 patients died of EAC, 6 who started with HGD and 2 who started with IMC. The overall mortality rate from EAC was 0.6 per 1000 PY. These results demonstrate that EAC and death from EAC were rare events after treatment with RFA, that the majority of patients who developed EAC after treatment with RFA had HGD at baseline, and all patients who died of EAC had HGD or IMC at baseline. Compared to historical controls, EAC incidence was diminished in every baseline histology grade, with a 5–10-fold risk reduction in subjects with non-dysplastic BE.

GERD: Effectiveness of Electrical Stimulation of the Lower Esophageal Sphincter in Refractory Disease

Electrical stimulation therapy (EST) of the lower esophageal sphincter (LES) is a novel therapy to increase the tone of the LES with the goal of reducing reflux events and esophageal acid exposure. A multi-center group examined patients with GERD partially responsive to PPI (>5 point improvement in GERD Health-Related Quality of Life (HRQL) on PPI). Included subjects had an LES end expiratory pressure of >5 mmHg, esophageal acid exposures of at least 5% of pH-metry time with pH <4 , hiatal hernia <3 cm, and less

than LA grade C esophagitis.[12] In 33 patients meeting those criteria, an electrical stimulator was implanted laparoscopically, with electrodes placed on the serosal surface of the GE junction. Stimulation was provided at 30 minute intervals 12 times per day, at 20 Hz and 5 mAmp.

From an on-PPI GERD HRQL average score of 15, patients improved to a mean of 4 at 3 months and 5 at 6 months. (Figure 3) Average percent of time with pH <4 improved from 10% at baseline to 4% at 3 months and 5% at 6 months. Notably, 89% of patients were off PPI at 6 months. There was a relatively high frequency of adverse events, with 89 adverse events occurring in 27 patients. However none were unanticipated, and most were typical of a surgical implant procedure, including incisional discomfort and post-operative nausea. Thirty-six adverse events were device, procedure, or therapy related. There were two serious adverse events: a small bowel perforation during implantation and an AV reentrant tachycardia requiring ablation (described as not device or procedure related). Other adverse events included pocket pain, and dysphagia. While these results demonstrate impressive effectiveness in reducing symptoms, acid exposure, and PPI use, additional investigation is required to determine the role of this device in clinical practice. Given the high prevalence of GERD incompletely responsive to PPI therapy, alternative therapies for this group are desirable, and early data on this procedure suggest that a device such as the one investigated here may be a viable alternative.

Functional Heartburn and Esophageal Hypersensitivity: Imipramine No Better Than Placebo

While antidepressants, particularly tricyclics, have broad use in functional gastrointestinal disorders, the utility of these medications in functional esophageal disorders has been understudied. A group from Thailand conducted a randomized, double blinded, placebo-controlled trial to assess the effectiveness of imipramine for esophageal hypersensitivity and functional heartburn.[13] They recruited 83 patients with EGD and 24-hour impedance pH monitoring consistent with esophageal hypersensitivity or functional heartburn. Patients were randomly assigned to 8 weeks imipramine 25mg at bedtime or placebo. The authors assessed GERD score and quality of life (QoL, measured with the SF-36) at baseline and 4 and 8 weeks. There was no difference at baseline between the imipramine (n=43) and placebo (n=40) groups on demographic or disease characteristics. Sixty-seven patients completed the trial. Eight discontinued the medication due to perceived side effects (6 in the imipramine group, 2 in the placebo group), and 8 did not adhere to the protocol. In an intention-to-treat analysis, there was no difference in response rates with 37% of patients in both groups achieving the primary end-point of a 50% decrease in GERD score at 8 weeks compared to baseline. There was no difference in response based on esophageal hypersensitivity or functional heartburn. There was also no difference in QoL by intent-to-treat analysis. There was greater constipation in the imipramine group (51% vs 22, p=0.01). These results, derived from a well-designed study, show no benefit and some harm—in the form of anticholinergic side effects—from the use of imipramine as compared to placebo for the treatment esophageal hypersensitivity and functional heartburn. Given the common use of this class of agents in subjects with functional GERD disorders, these data should make

clinicians question their routine use in this clinical setting. This negative study also highlights the need for novel therapeutic options in this difficult to treat patient group.

Achalasia: Increasing Experience with Peroral Endoscopic Myotomy

The optimal management of achalasia remains debated, and surgical myotomy, pneumatic dilatation, and endoscopic myotomy have all been proposed as initial strategies. The use of peroral endoscopic myotomy (POEM) for the treatment of achalasia and associated motility disorders has been increasing, though the technique remains somewhat controversial, and awaits widespread acceptance. One of the pioneers of the procedure, Dr. Haruhiro Inoue, and a team from Japan presented data evaluating POEM for the treatment of achalasia and other spastic/hypertensive motility disorders.[14] They prospectively enrolled 500 consecutive patients who underwent the procedure between 2008–13. Patients ranged in age from 3 to 87 with a mean of 45 years. Subjects in the trial had symptoms for 0.4 to 63 years prior to treatment (mean 11 years). The POEM procedure took an average of 98 minutes, myotomy length averaged 14 cm, and no procedure had to be converted to an open surgery. No major complications occurred, though notable adverse events occurred in a total of 3% of patients and included mucosal injury (n=8), submucosal hematoma (n=3), pleural effusion (n=2), pneumothorax (n=1), peritonitis (n=1), and bleeding requiring transfusion (n=1). Post-procedure, 95% of patients had an Eckardt score of <3. Overall, 16% of subjects developed symptomatic GERD, but only 5% required PPI therapy. For 36 patients followed more than 3 years, the average Eckardt score after 3 years was 2.3 compared to 6.6 at baseline. These results indicate that POEM is effective and durable when performed at an expert center. The choice of POEM as a primary modality for management of achalasia will likely depend on local expertise with the various forms of management of this disease. These data suggest that tertiary centers with expertise in endoscopic therapy may be able to provide this modality with results comparable to or better than traditional modes of management of achalasia. Issues of training and certification for this procedure will need to be addressed prior to wide implementation of this approach in the U.S.

Squamous Cell Carcinoma of the Esophagus: Biomarkers Show Promise for Screening

Squamous cell carcinoma (SCC) remains the predominant esophageal malignancy of the developing world, and 5-year survival is less than 10%. The incidence of SCC of the esophagus is high enough in some areas of Asia that endoscopic screening is performed. Predictors of dysplasia, and markers of neoplastic progression that do not depend on morphological analysis of tissue biopsies are lacking.

In this setting, Dr. Redman et al tested biomarkers for SCC.[15] Through mining of a publically available dataset, researchers identified 800 genes overexpressed in SCC compared to normal esophagus with $p < 10^{-5}$. Of the top 50 genes, 18 were overexpressed in the stroma or normal esophagus. Researchers used qPCR in samples from 60 normal esophagi and 30 with SCC and identified 21 genes significantly overexpressed in SCC. They then performed immunohistochemistry in 60 normal esophagi and 30 each with mild, moderate, and severe dysplasia, and SCC to assess dysregulated gene expression for the six

(CHN1, COL3A1, CTSL, TNFAIP3, and TNC) which demonstrated the best discrimination between normal esophagus and SCC. Of these, CHN1 and TNFAIP3 showed increased staining corresponding to increased dysplasia. (Figure 4) Expression of p53 also increased with increasing dysplasia. These data suggest that these three markers, perhaps taken in conjunction with other clinical and endoscopic variables, may be able to stratify patients based on degree of dysplasia and risk for SCC. While these findings are provocative, in vivo testing of high risk individuals is still needed.

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Figure 1. Specimens obtained from the Cytosponge from two patients demonstrating the extensive amount of tissue that can be obtained with this technique. Panels (A) and (C) show esophageal tissue samples stained with routine H&E for each of the patients. Panels (B) and (D) show markedly increased immunohistochemical staining for eotaxin-derived neurotoxin for the same specimens. Courtesy of David Katzka.

Figure 2. Sample obtained by WATS demonstrating high grade dysplasia with nuclear hyperchromasia, irregular thick nuclear membranes, increased nuclear to cytoplasmic ratio, overlapping nuclei, and loss of nuclear polarity. Courtesy of Seth Gross.

Sustained Improvement in Esophageal Acid Exposure

*Statistically significant and sustained improvement in Esophageal Acid Exposure vs. Baseline at 6 months ($p < 0.001$) and 12 months ($p < 0.001$). Data: Medians, IQR.

Sustained Improvement in GERD Symptoms

*Statistically significant and sustained improvement in patients GERD-HRQL score vs. Baseline On and Off-PPI scores ($p < 0.001$ for all visits vs. Baseline Off-PPI; $p < 0.005$ at 6 mo. vs. Baseline On-PPI; $p < 0.05$ at 12 mo vs. Baseline On-PPI). Data: Medians, IQR.

Figure 3.

(L) Median hours with distal esophageal pH <4 prior to implantation of electrical stimulator (gray) and at six- and twelve-months post-implantation (blue). (R) Median GERD-HRQL Scores on and off PPI (gray) and six- and twelve-months after implantation (blue). Error bars represent interquartile range. Courtesy of Peter Siersma.

Figure 4. Immunohistochemical staining demonstrates increased staining for CHN1 and TNFAIP3 with dysplasia and malignant transformation. Courtesy of Pierre Lao-Sirieix.

Table 1

Incidence and Mortality of EAC After RFA

Baseline Histology	Patients n (%)	Patient-Years of Follow-up	Incident EAC Cases n	EAC Incidence Rate per 1000 person-years [95% CI]	Deaths from EAC n	EAC Mortality Rate per 1000 person-years [95% CI]
NDBE	2,472 (48)	6,279	3	0.5 [0.2, 1.4]	0	0 [0, 0.6]
IND	388 (8)	959	2	2.1 [0.3, 7.5]	0	0 [0, 3.8]
LGD	1,053 (21)	2,802	11	3.9 [2.0, 7.0]	0	0 [0, 1.3]
HGD	978 (19)	2,782	84	30.2 [24.1, 37.4]	6	2.2 [0.8, 4.7]
Total, non-malignant	4,891 (95)	12,822	100	7.8 [6.3, 9.5]	6	0.5 [0.2, 1.0]
IMC	180 (4)	498	--	--	2	4.0 [0.5, 14.5]
IAC	61 (1)	163	--	--	0	0 [0, 22.6]
Total	5,132 (100)	13,483	--	--	8	0.6 [0.3, 1.2]